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# Flow Mediate Dilation of Brachial Artery; Endothelial Dysfunction and Stroke

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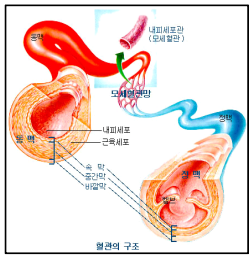
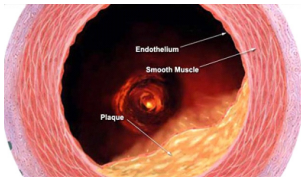
## Endothelium

- Single cell lining covering inner surface of blood vessel
- Role; maintain blood fluidity and vascular health
- Turn over time of endothelium
  > 3 years in adult mice



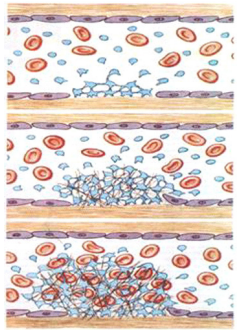
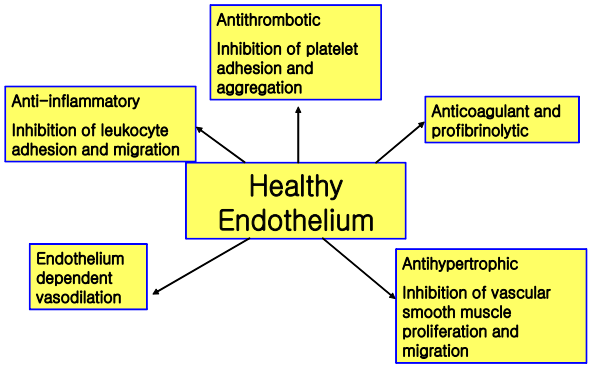



**Table 1.** Normal Functions of the Vascular Endothelium and a Partial List of Factors Elaborated and Regulated by the Endothelium to Maintain Vascular Homeostasis

| |
|---|
| Maintenance of vascular tone |
| Nitric oxide |
| Prostaglandins (prostacyclin [$PGI_2$], thromboxane $A_2$ [$TxA_2$]) |
| Endothelial hyperpolarizing factor |
| Endothelin-1 |
| Angiotensin II |
| C-type natriuretic peptide |
| Balancing blood fluidity and thrombosis |
| Nitric oxide |
| Tissue plasminogen activator |
| Heparins |
| Thrombomodulin |
| Prostaglandins |
| Plasminogen activator inhibitor-1 (PAI-1) |
| Tissue factor |
| Von Willibrand's factor |
| Control of the vascular inflammatory process |
| Monocyte chemotactic factor-1 (MCP-1) |
| Adhesion molecule expression (VCAM-1, ICAM-1, selectins) |
| Interleukins 1, 6, and 18 |
| Tumor necrosis factor |

ICAM-1 = intercellular adhesion molecule-1; VCAM-1 = vascular cell adhesion molecule-1.

## Endothelial Function



## Endothelium-derived NO

- Leukocyte adhesion and infiltration into arterial wall is an essential step in atherosclerotic lesion formation
- Regulated by leukocyte adhesion molecule
- Pharmacological inhibition of endothelium derived NO lead to marked increase of adhesiveness for monocyte.
  Attenuated by L-arginin, substrate of eNOS
- In eNOS deficiency mice, leukocyte – endothelial cell interaction increase
- Inhibition of eNOS results in increased expression of leukocyte adhesion molecules and critical chemokines, such as monocyte chemoattractant protein -1

## Endothelium-derived NO

Vasodilatation,
Inhibit the release of ET-1
smooth muscle proliferation
leukocyte adhesion
platelet aggregation
tissue factor production

## Mechanism of Endothelial Dysfunction

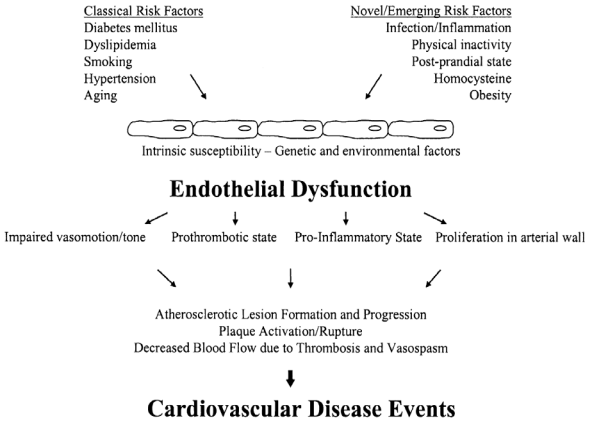
- Endothelial dysfunction is a multifactorial process
  Production of reactive oxygen species

  superoxide ↑ in atherosclerosis and coronary disease
  superoxide + NO → peroxynitrate & loss of bioactive NO
  superoxide + BH4 (eNOS cofactor) → eNOS uncoupling
  → ↓NO, ↑superoxide
  redox sensitive inhibition of dimethylarginine dimethylanimohydrolase (DDAH) → ↑eNOS inhibitor (asymmetric dimethylarginine, ADMA)

Other source of superoxide: NADPH oxidase, (BH4 를 산화 → uncoupling)
Xanthin oxidase

## Mechanism of Endothelial Dysfunction

- Superoxide dismutase (SOD)
  vascular superoxide level is regulated not by its production but its degradation.
- Extracelluar form of SOD (ecSOD) ;
  mainly located between ednothelium and smooth muscle
  NO induces ecSOD expression in arterial wall.
  if NO↓→ ecSOD↓→ superoxide↑→ endothelial dysfucntion




## Assessment of Endothelial Function

### Methods to Quantify Endothelial Function

- Intracoronary agonist infusion with quantitative coronary angiography
- Brachial artery catheterization with venous occlusive plethysmography
- Vascular tonometry and measurement of vascular stiffness
- Brachial artery Ultrasonography with FMD

### Serum markers of endothelial dysfunction

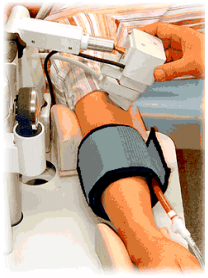
- Plasminogen activator inhibitor -1
- Endothelin
- Adhesion molecules (VCAM, ICAM)

## Assessment of Endothelial Function

- Enodthelium Dependent Vasodilation
  - to Ach
  - to Flow

Conduit artery; 직경을 측정

Resistance artery; flow velocity



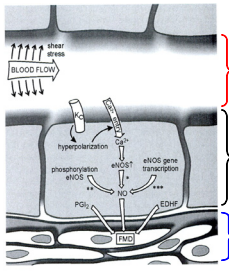
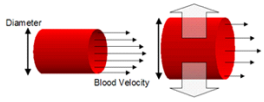
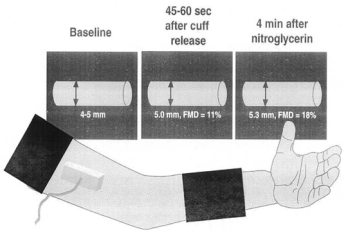
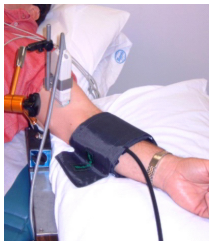



Figure 1. The genesis of FMD, in response to different changes in shear stress. * = very short-term changes; ** = changes taking place over slightly longer periods (minutes); *** = changes taking place over a longer time (many minutes or hours). $PGI_2$ = prostacyclin; EDHF = endothelium-derived hyperpolarizing factor; Kc = calcium-activated potassium channel.

Arterial occlusion
↓
Ischemia
↓
Reactive Dilation
↓
Flow Velocity ↑
↓
Shear Stress ↑
↓
Induce eNOs

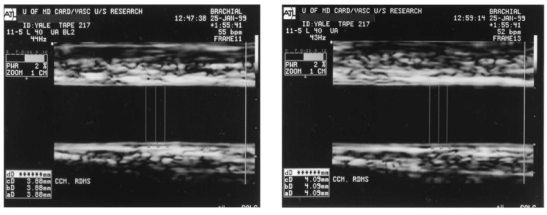


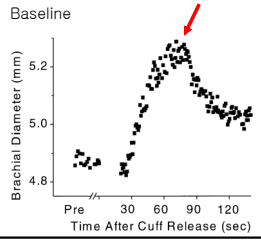
FMD is measured as the percentage change in brachial diameter from the baseline in response to the increased flow.

(J Am Coll Cardiol 2002;39:257–65)



Baseline

After reactive hyperemia




(J Am Coll Cardiol 2002;39:257–65)

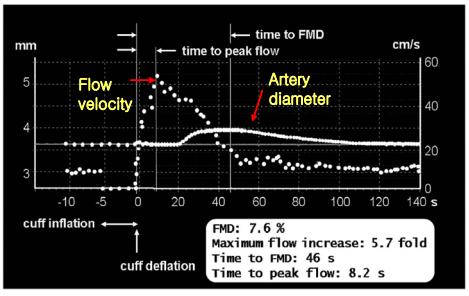



**Fig. 3.** ***A continuous recording of brachial artery diameter and blood flow velocity during cuff inflation and after cuff deflation.***
*The FMD indicates the endothelial function of the conduit artery, while the maximum blood flow response indicates that of the resistance vessels, although FMD is also indirectly affected by the endothelial function of the resistance vessels. In addition to FMD and the maximum blood flow increase, the time to maximum response for FMD or blood flow may also be used as indices of endothelial function.*

*Hypertens Res Vol. 31, No. 12 (2008)*

**Table 1. Flow-Mediated Vasodilation (FMD) *vs.* Nitroglycerine Vasodilation (NTGD)**

| FMD | NTGD | Vascular function |
|---|---|---|
| → | → | Normal |
| ↓↑→ | ↓ | Smooth muscle dysfunction, change in vascular structure |
| ↓ | → | Endothelial dysfunction |

*Hypertens Res Vol. 31, No. 12 (2008)*

## Potential link between endothelial dysfunction and vascular event

- Endothelial dysfucntion represent cumulative effects of traditional risk factors on vascularture.
- Endothelial dysfunction reflects the presence and extent of atherosclerosis.
- Various endothelial function in patients with atherosclerosis

- Inability to limit local shear stress at the arterial wall
- Loss of anti-inflammatory effect
  - anti-platelets effect
  - anti-fibrinolytic factor
  - pro-inflammatory factors

## Endothelial Function and Vascular Event

- Increased cerebrovascular risk impaired FMD in Pt with HET
- TIA less frequent in improved FMD in HET
- Frequent CVD in patient with low FMD over 4.5 F-U years
- 5 year prognosis in patient with chest pain
  more CVD in patients with <10% FMD

## Predictive Value of Endothelial Dysfunction

**Table 3.** Studies Evaluating the Predictive Value of Endothelial Dysfunction

| Lead Author | Design/ Mean Follow-Up | Patient Population | Vascular Bed | Marker of Endothelial Function | End Points Examined | Findings |
|---|---|---|---|---|---|---|
| Al Suwaidi (27) | Retrospective/28 months | 157 patients with mild CAD | Coronary | Acetylcholine response | Cardiac death, MI, CHF, CABG, or PCI | 6 patients with event. Acetylcholine response independent predictor of events. |
| Schachinger (28) | Retrospective/7.7 years | 147 patients with CAD | Coronary | Acetylcholine, cold pressor test, FMD, NTG | MI, UA, ischemic stroke, CABG, PTCA, peripheral bypass | 29 patients with event. Vasomotor function independent predictor of events. |
| Neunteufl (31) | Retrospective/5 years | 73 patients with CAD | Brachial | FMD | Death, MI, PTCA, or CABG | 27 patients with event. FMD <10% predictive of events. Effect lost when controlling for extent of CAD |
| Heitzer (30) | Prospective/4.5 years | 291 patients with CAD | Brachial | Forearm blood flow response to acetylcholine | CVD death, stroke, MI, CABG, PTCA, peripheral bypass | 91 patients with event. Acetylcholine response independent predictor of events. |
| Perticone (34) | Prospective/32 months | 225 patients with hypertension | Brachial | Forearm blood flow response to acetylcholine | CVD death, MI, stroke, TIA, UA, CABG, PTCA, PVD | 29 subjects with event. Acetylcholine response predictive of events. |
| Gokce (32) | Prospective/30 days | 187 patients undergoing vascular surgery | Brachial | FMD | CVD death, MI, UA, stroke | 45 patients with event. FMD independent predictor of events. |
| Modena (35) | Prospective/67 months | 400 hypertensive post-menopausal women | Brachial | FMD | Hospitalization for CVD event (not otherwise specified) | 47 patients with event. Failure to improve FMD with 6 months of antihypertensive therapy independent predictor of events. |
| Halcox (29) | Retrospective/46 months | 308 patients referred for cardiac catheterization | Coronary | Acetylcholine response | CVD death, MI, ischemic stroke, UA | 35 subjects with event. Acetylcholine response independent predictor of events. |
| Schindler (36) | Prospective/45 months | 130 patients with normal coronary angiograms | Coronary | Cold pressor test | CVD death, UA, MI, PTCA, CABG, stroke, peripheral bypass | 26 patients with event. Cold pressor test response independent predictor of events. |
| Gokce (33) | Prospective/1.2 years | 199 patients undergoing vascular surgery | Brachial | FMD | CVD, death, MI, UA, stroke | 35 patients with events. FMD independent predictor of long-term events. |

CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; CHF = congestive heart failure; CVD = cardiovascular disease; FMD = flow-mediated dilation; MI = myocardial infarction; NTG = nitroglycerin-mediated dilation; PCI = percutaneous coronary intervention; PTCA = percutaneous transluminal coronary angioplasty; PVD = peripheral vascular disease; TIA = transient ischemic attack; UA = unstable angina.

## Endothelial Dysfunction in Stroke

***Table 2*** *Comparisons of clinical profiles and laboratory findings among control and different stroke subtypes*

| | Control, n = 40 | Large-artery atherosclerosis, n = 40 | Cardioembolism, n = 21 | Lacunar infarction, n = 56 | Undetermined etiology, n = 26 | *p* Value |
|---|---|---|---|---|---|---|
| Age, years | 66.7 ± 8.3 | 67.8 ± 8.2 | 67.6 ± 9.2 | 67.6 ± 10.2 | 70.0 ± 9.2 | 0.711 |
| Sex, F/M | 13/27 | 8/32 | 6/15 | 12/44 | 6/20 | 0.678 |
| Diabetes, % | 5 (13%) | 17 (43%) | 10 (48%) | 16 (29%) | 11 (42%) | 0.012 |
| Hypertension, % | 6 (15%) | 23 (58%) | 14 (67%) | 37 (66%) | 9 (35%) | <0.001 |
| Hyperlipidemia, % | 10 (20%) | 8 (20%) | 7 (33%) | 13 (23%) | 4 (15.4%) | 0.660 |
| Coronary artery disease, % | 4 (10%) | 19 (48%) | 16 (76%) | 17 (30%) | 6 (23%) | <0.001 |
| Previous stroke, % | 0 (0%) | 13 (33%) | 4 (19%) | 5 (9%)† | 5 (19%) | <0.001 |
| Smoking, % | 7 (18%) | 13 (33%) | 3 (14%) | 16 (29%) | 8 (31%) | 0.354 |
| Systolic blood pressure, mm Hg | 119.5 ± 14.9 | 141.9 ± 22.2* | 142.8 ± 19.7* | 144.1 ± 23.1* | 131.8 ± 15.1* | <0.001 |
| Diastolic blood pressure, mm Hg | 70.0 ± 13.4 | 73.7 ± 10.4 | 84.8 ± 16.0*† | 81.5 ± 14.5* | 76.0 ± 9.2 | <0.001 |
| Fasting plasma sugar, mg/dL | 104.5 ± 37.4 | 120.8 ± 54.5 | 121.0 ± 41.2 | 102.3 ± 38.8 | 125.5 ± 68.8 | 0.121 |
| Triglyceride, mg/dL | 131.6 ± 69.5 | 149.9 ± 74.4 | 156.7 ± 87.1 | 144.8 ± 92.4 | 138.1 ± 86.8 | 0.726 |
| Low-density lipoprotein cholesterol, mg/dL | 105.4 ± 46.7 | 107.2 ± 36.0 | 111.6 ± 49.6 | 108.6 ± 42.0 | 96.1 ± 43.7 | 0.744 |
| High-density lipoprotein cholesterol, mg/dL | 39.0 ± 12.7 | 42.1 ± 16.5 | 34.6 ± 12.8 | 37.9 ± 12.7 | 41.7 ± 15.7 | 0.271 |
| Flow-mediated dilation, % | 8.8 ± 6.0 | 5.7 ± 5.4 | 5.6 ± 5.0 | 4.3 ± 6.1* | 6.1 ± 6.3 | 0.008 |
| Current medication | | | | | | |
| Antiplatelets/warfarin | 12/0 | 39/1 | 8/13 | 56/0 | 24/2 | <0.001 |
| OHA/insulin | 3/0 | 12/5 | 8/2 | 13/3 | 9/2 | 0.002 |
| Statins/fibrate | 6/4 | 6/2 | 4/2 | 8/5 | 1/3 | 0.853 |
| ACEI or ARB | 4 | 15 | 8 | 22 | 3 | 0.003 |
| Calcium channel blocker | 3 | 12 | 5 | 15 | 5 | 0.124 |
| Other antihypertensive agents | 1 | 5 | 4 | 8 | 2 | 0.259 |

*$p < 0.01$ compared with control group.
†$p < 0.05$ compared with large-artery atherosclerosis group.

OHA = oral hypoglycemic agent; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker.



## Impaired Endothelial Function of Forearm Resistance Arteries in CADASIL patients

**Table 2. Mean Values and SD Are Given for Continuous Variables**

| Method | Variable | CADASIL-Patients | Controls | *P* Value |
|---|---|---|---|---|
| Invasive | Forearm Blood Flow, baseline, ml/min/100 mL tissue | 3.4±0.9 | 4.8±1.9 | 0.034 |
| Invasive | Forearm Blood Flow, SNP 5 μg/minute | 11.3±3.0 | 15.2±8.0 | 0.190 |
| Invasive | Forearm Blood Flow, SNP 10 μg/minute | 15.3±4.8 | 20.8±10.4 | 0.166 |
| Invasive | Forearm Blood Flow, Ach 25 μg/minute | 14.5±8.2 | 23.3±12.0 | 0.061 |
| Invasive | Forearm Blood Flow, Ach 50 μg/minute | 21.3±8.6 | 32.1±12.0 | 0.023 |
| Invasive | Endothelial function index | 1.21±0.44 | 1.62±0.48 | 0.007 |
| Ultrasound | Flow mediated dilation, % | 6.8±5.0 | 6.6±2.9 | 0.924 |
| Ultrasound | Maximal velocity of blood flow, baseline, m/s | 0.84±0.13 | 1.00±0.22 | 0.046 |
| Ultrasound | Maximal velocity of blood flow, hyperemia, m/s | 1.75±0.21 | 2.01±0.26 | 0.011 |
| Pulse wave | Baseline reflection index, % | 44.6±8.9 | 44.1±5.6 | 0.867 |
| Pulse wave | Reflection index efter terbutaline, % | 28.9±7.3 | 31.2±6.7 | 0.395 |
| Pulse wave | Change in reflection index, % | -34.6±10.4 | -29.0±12.5 | 0.238 |

SNP indicates sodium nitroprusside; Ach, Acetylcholine.

(*Stroke*. 2007;38:2692-2697.)

## Lacunar Infarction and Systemic Endothelial Dysfunction

| | Group A, stroke patients | Group B, patients with risk factors | Group C, Healthy volunteers |
|---|---|---|---|
| IMT (mm) | 0.86 ±0.18 | 0.82 ± 0.16 | 0.64 ± 0.15* |
| Flow-Mediate dilatation(%) | 0.4 ± 5.0** | 3.8 ± 4.8** | 7.9 ± 6.0* |

Acta neurol scand 2006:113:273

## Cerebrovascular Reactivity to *L*-Arginine in Patients with Lacunar Infarctions

| | Group A Stroke patients | Group B Subjects with risk factors | Group C Healthy volunteers |
|---|---|---|---|
| $v_m$ at rest, cm/s<br>vm after *L*-arginine, cm/s | 52.7 ± 15.7<br>60.1 ± 19.5[a] | 54.1 ± 13.2<br>60.1 ± 15.4[a] | 52.6 ± 16.2<br>62.8 ± 19.8[a] |
| MAP at rest, mm Hg<br>MAP after *L*-arginine, mm Hg | 103.6 ± 14.3[b]<br>102.3 ± 14.3 | 100.2 ± 7.6<br>98.7 ± 7.8 | 98.3 ± 5.1<br>98.3 ± 7.1 |
| HR at rest, beats/min<br>HR after *L*-arginine, beats/min | 67.1 ± 9.8<br>68.9 ± 10.7[a] | 63.3 ± 11.3<br>65.2 ± 11.5[a] | 62.7 ± 10.9<br>65.5 ± 6.7[a] |
| $CO_2$ at rest, mm Hg<br>$CO_2$ after *L*-arginine, mm Hg | 18.5 ± 4.8[b]<br>17.7 ± 5.2[a] | 15.9 ± 2.6<br>16.1 ± 2.2 | 16.5 ± 3.0<br>16.3 ± 2.8 |
| Et-$CO_2$ at rest, mm Hg<br>Et-$CO_2$ after *L*-arginine, mm Hg | 28.5 ± 5.7<br>27.8 ± 5.7[a] | 29.7 ± 3.5<br>29.9 ± 3.4 | 30.4 ± 3.7<br>29.9 ± 2.7 |

$CO_2$ = Partial pressure of carbon dioxide. [a] $p \leq 0.01$: comparison between values before and after *L*-arginine infusion; [b] $p \leq 0.05$: comparison among groups A, B and C.

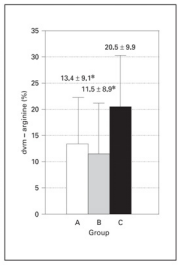



**Fig. 2.** Comparison of cerebral endothelial function among the three groups; dvm – arginine = relative difference between the $v_m$ in the MCA before and after L-arginine infusion. * $p < 0.01$: comparison between groups A, B and C.

Cerebrovasc Dis 2006;21:180.186

## Endothelial Function in Lacunar Infarction: a comparison of lacunar infarction, cerebral atherosclerosis and control group

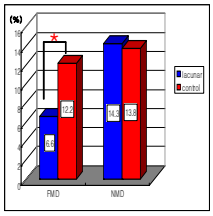



**Fig. 1.** FMD was lower in patients with LI compared to the control group (*p = 0.000). NMD was similar in both groups (p = 0.620). LI = Lacunar infarction.

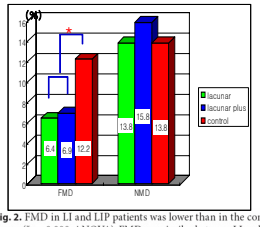



**Fig. 2.** FMD in LI and LIP patients was lower than in the control group (*p = 0.000, ANOVA). FMD was similar between LI and LIP patients. NMD was not different among LI, LIP and the control group. LI = Lacunar infarction; LIP = lacunar infarction plus.

YS Kim, Cerebrovasc Dis 2009;28:166–170

## Relationship between Circulating Endothelial Progenitor Cells and Endothelial Dysfunction in patients with Cerebral Small Vessel Disease

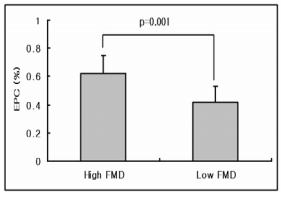



Figure 2. The number of circulating EPCs in peripheral blood of patients with High and low FMD.

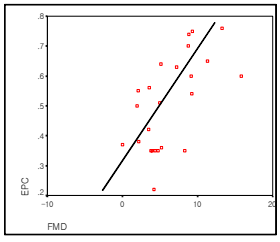



Figure 3. Relation between circulating EPC and FMD in patients with cerebral small vessel disease ($R^2$: 0.383 p=0.001)

Unpublished data 2007

## Influence of Atorvastatin Treatment on L-Arginine Cerebrovascular Reactivity and Flow-Mediated Dilatation in Patients With Lacunar Infarctions

**TABLE 3. Comparison of Cerebrovascular Reactivity to L-Arginine and FMD at Study Onset and After 3 Months, During Which Group A and Group B Patients Received Treatment With Atorvastatin**

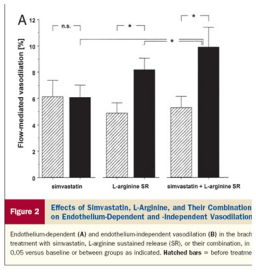
| | Group A Stroke Patients | Group B Patients With Similar Risk Factors | Group C Healthy Volunteers |
|---|---|---|---|
| L-arginine reactivity | 13.1±8.4% | 13.5±8.3% | 21.3±10.9%** |
| L-arginine reactivity after 3 months | 17.1±7.6%* | 18.2±11.0%* | 20.2±10.2% |
| FMD | 0.06±4.9% | 3.1±4.8% | 8.1±6.0%** |
| FMD after 3 months | 7.0±5.7%* | 5.3±3.6%*,** | 8.7±4.7%** |

*Comparison between values before and after atorvastatin treatment (Groups A and B; $P \leq 0.01$); **Comparison between values of Groups A, B and C ($P \leq 0.05$).

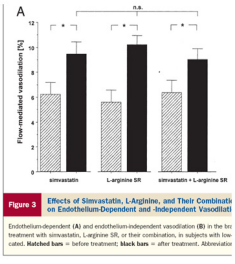
(*Stroke*. 2006;37:2540–2545.)

## Asymmetric Dimethylarginine Determines the Improvement of Endothelium-Dependent Vasodilation by Simvastatin

(J Am Coll Cardiol 2007;49:2274.82)




High ADMA




Low ADMA

**Table 4.** Effect of Interventions on Endothelial Function and CVD

| Intervention | Effect on Endothelial Function | Effect on CVD Events |
|---|---|---|
| Lipid-lowering therapy | + | + |
| Smoking cessation | + | + |
| Exercise | + | + |
| ACE inhibitors | + | + |
| Angiotensin receptor blockers | + | + |
| N-3 fatty acids | + | + |
| Glycemic control in diabetes mellitus | + | + |
| Hormone replacement therapy | ± | − |
| Vitamin E | ± | − |
| Combination antioxidants | − | − |
| L-arginine | + | ? |
| Dietary flavonoids | + | ? |
| Vitamin C | + | ? |
| Folate | + | ? |
| Tetrahydrobiopterin | + | ? |
| Specific metal ion chelation therapy | + | ? |
| Protein kinase C inhibition | + | ? |
| Cyclooxygenase-2 inhibition | + | ? |
| Thromboxane $A_2$ inhibition | + | ? |
| Troglitazone treatment in diabetes | + | ? |
| Xanthine oxidase inhibition | + | ? |
| Tumor necrosis factor inhibition | + | ? |

+ = weight of evidence indicates an improvement; − = weight of evidence indicates no effect or worsening; ? = there are insufficient data at the present time.
ACE = angiotensin converting enzyme; CVD = cardiovascular disease.

## Clinical Value of FMD

- FMD may be a **noninvasive means** of assessing endothelial function. (r=0.78,p<0.001)
- Impaired FMD is associated with cardiovascular disease and its major risk factors, and improved with pharmacological agents of known benefit in cardiovascular disease.
- FMD provides significant diagnositic and prognositc information in patients either with or at risk for CAD.
  In suspected CAD, brachial artery FMD<4.5% has sensitivity, specificity and PPV of 71%, 81%, and 95%.
  FMD>10% has NPP of 95% for ischemia as detected with exercise myocardial perfusion image.
- Possible association between SVD and endothelial function